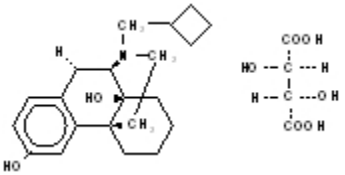
BUTORPHANOL TARTRATE - butorphanol tartrate spray, metered
Roxane Laboratories, Inc

RX ONLY

DESCRIPTION

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl)morphinan-3,14-diol [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt). The molecular formula is $C_{21}H_{29}NO_2 \bullet C_4H_6O_6$, which corresponds to a molecular weight of 477.55 and the following structural formula:



Butorphanol tartrate is a white crystalline substance. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

Butorphanol Tartrate Nasal Spray USP is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. Each bottle of Butorphanol Tartrate Nasal Spray USP contains 2.5 mL of a 10 mg/mL solution of butorphanol tartrate with sodium chloride, citric acid, and benzethonium chloride in purified water with sodium hydroxide and/or hydrochloric acid added to adjust the pH to 5.0. The pump reservoir must be fully primed (see **PATIENT INSTRUCTIONS**) prior to initial use. After initial priming each metered spray delivers an average of 1.0 mg of butorphanol tartrate and the 2.5 mL bottle will deliver an average of 14 to 15 doses of Butorphanol Tartrate Nasal Spray USP. If not used for 48 hours or longer, the unit must be reprimed (see **PATIENT INSTRUCTIONS**). With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8 to 10 doses of Butorphanol Tartrate Nasal Spray USP depending on how much repriming is necessary.

CLINICAL PHARMACOLOGY

General Pharmacology and Mechanism of Action

Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). It is also an agonist at the κ-opioid receptors.

Its interactions with these receptors in the central nervous system apparently mediate most of its pharmacologic effects, including analgesia.

In addition to analgesia, CNS effects include depression of spontaneous respiratory activity and cough, stimulation of the emetic center, miosis, and sedation. Effects possibly mediated by non-CNS mechanisms include alteration in cardiovascular resistance and capacitance, bronchomotor tone, gastrointestinal secretory and motor activity, and bladder sphincter activity.

In an animal model, the dose of butorphanol tartrate required to antagonize morphine analgesia by 50% was similar to that for nalorphine, less than that for pentazocine and more than that for naloxone.

The pharmacological activity of butorphanol metabolites has not been studied in humans; in animal studies, butorphanol metabolites have demonstrated some analgesic activity.

In human studies of butorphanol (see **Clinical Trials**), sedation is commonly noted at doses of 0.5 mg or more. Narcosis is produced by 10 to 12 mg doses of butorphanol administered over 10 to 15 minutes intravenously.

Butorphanol, like other mixed agonist-antagonists with a high affinity for the κ-receptor, may produce unpleasant psychotomimetic effects in some individuals.

Nausea and/or vomiting may be produced by doses of 1 mg or more administered by any route.

In human studies involving individuals without significant respiratory dysfuction, 2 mg of butorphanol IV and 10 mg of morphine sulfate IV depressed respiration to a comparable degree. At higher doses, the magnitude of respiratory depression with butorphanol is not appreciably increased; however, the duration of respiratory depression is longer. Respiratory depression noted after administration of butorphanol to humans by any route is reversed by treatment with naloxone, a specific opioid antagonist (see **Treatment**in **OVERDOSAGE**section).

Butorphanol tartrate demonstrates antitussive effects in animals at doses less than those required for analgesia.

Hemodynamic changes noted during cardiac catheterization in patients receiving single 0.025 mg/kg intravenous doses of butorphanol have included increases in pulmonary artery pressure, wedge pressure and vascular resistance, increases in left ventricular end diastolic pressure, and in systemic arterial pressure.

Pharmacodynamics

The analgesic effect of butorphanol is influenced by the route of administration. Onset of analgesia is within a few minutes for intravenous administration, within 15 minutes for intramuscular injection, and within 15 minutes for the nasal spray doses.

Peak analgesic activity occurs within 30 to 60 minutes following intravenous and intramuscular administration and within 1 to 2 hours following the nasal spray administration.

The duration of analgesia varies depending on the pain model as well as the route of administration, but is generally 3 to 4 hours with IM and IV doses as defined by the time 50% of patients required remedication. In postoperative studies, the duration of analgesia with IV or IM butorphanol was similar to morphine, meperidine, and pentazocine when administered in the same fashion at equipotent doses (see Clinical Trials). Compared to the injectable form and other drugs in this class, butorphanol tartrate nasal spray has a longer duration of action (4 to 5 hours) (see **Clinical Trials**).

Pharmacokinetics

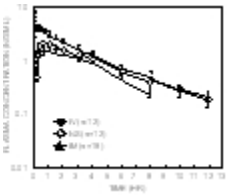
Butorphanol tartrate injection is rapidly absorbed after IM injection and peak plasma levels are reached in 20 to 40 minutes.

After nasal administration, mean peak blood levels of 0.9 to 1.04 ng/mL occur at 30 to 60 minutes after a 1 mg dose (see **Table 1**).

The absolute bioavailability of butorphanol tartrate nasal spray is 60 to 70% and is unchanged in patients with allergic rhinitis. In patients using a nasal vasoconstrictor (oxymetazoline) the fraction of the dose absorbed was unchanged, but the rate of absorption was slowed. The peak plasma concentrations were approximately half those achieved in the absence of the vasoconstrictor.

Following its initial absorption/distribution phase, the single dose pharmacokinetics of butorphanol by the intravenous, intramuscular, and nasal routes of administration are similar (see **Figure 1**).

Figure 1: Butorphanol Plasma Levels After IV, IM and Nasal Spray Administration of 2 mg Dose



Serum protein binding is independent of concentration over the range achieved in clinical practice (up to 7 ng/mL) with a bound fraction of approximately 80%.

The volume of distribution of butorphanol varies from 305 to 901 liters and total body clearance from 52 to 154 liters/hr (see **Table 1**).

Table 1: Mean Pharmacokinetic Parameters of Butorphanol in Young and Elderly Subjects*

	Intravenous		Nasal	
Parameters	Young	Elderly	Young	Elderly
T_{max}† (hr)			0.62 (0.32)‡ (0.15-1.50)§	1.03 (0.74) (0.25-3.00)
C_{max}¶ (ng/mL)			1.04 (0.40) (0.35-1.97)	0.90 (0.57) (0.10-2.68)
AUC (inf)# (hr·ng/mL)	7.24 (1.57) (4.40-9.77)	8.71 (2.02) (4.76-13.03)	4.93 (1.24) (2.16-7.27)	5.24 (2.27) (0.30-10.34)
Half-life (hr)	4.56 (1.67) (2.06-8.70)	5.61 (1.36) (3.25-8.79)	4.74 (1.57) (2.89-8.79)	6.56 (1.51) (3.75-9.17)
Absolute Bioavailability (%)			69 (16) (44-113)	61 (25) (3-121)
Volume of Distribution Þ (L)	487 (155) (305-901)	552 (124) (305-737)		
Total Body Clearance (L/hr)	99 (23) (70-154)	82 (21) (52-143)		

*****Young subjects (n=24) are from 20 to 40 years old and elderly (n=24) are greater than 65 years of age.
†Time to peak plasma concentration.
‡Mean (1 S.D.)
§(range of observed values)
¶Peak plasma concentration normalized to 1 mg dose.
#Area under the plasma concentration-time curve after a 1 mg dose.
ÞDerived from IV data.

Dose proportionality for butorphanol tartrate nasal spray has been determined at steady state in doses up to 4 mg at 6 hour intervals. Steady state is achieved within 2 days. The mean peak plasma concentration at steady state was 1.8-fold (maximal 3-fold) following a single dose.

The drug is transported across the blood brain and placental barriers and into human milk (see **PRECAUTIONS: Labor and Delivery** and Nursing Mothers sections).

Butorphanol is extensively metabolized in the liver. Metabolism is qualitatively and quantitatively similar following intravenous, intramuscular, or nasal administration. Oral bioavailability is only 5 to 17% because of extensive first pass metabolism of butorphanol. The major metabolite of butorphanol is hydroxybutorphanol, while norbutorphanol is produced in small amounts. Both have been detected in plasma following administration of butorphanol, with norbutorphanol present at trace levels at most time points. The elimination half-life of hydroxybutorphanol is about 18 hours and, as a consequence, considerable accumulation (~5-fold) occurs when butorphanol is dosed to steady state (1 mg transnasally q6h for 5 days).

Elimination occurs by urine and fecal excretion. When ^{3}H labelled butorphanol is administered to normal subjects, most (70 to 80%) of the dose is recovered in the urine, while approximately 15% is recovered in the feces.

About 5% of the dose is recovered in the urine as butorphanol. Forty-nine percent is eliminated in the urine as hydroxybutorphanol. Less than 5% is excreted in the urine as norbutorphanol.

Butorphanol pharmacokinetics in the elderly differ from younger patients (see **Table 1**). The mean absolute bioavailability of butorphanol tartrate nasal spray in elderly women (48%) was less than that in elderly men (75%), young men (68%), or young women (70%). Elimination half-life is increased in the elderly (6.6 hours as opposed to 4.7 hours in younger subjects).

In renally impaired patients with creatinine clearances <30 mL/min, the elimination half-life was approximately doubled and the total body clearance was approximately one half (10.5 hours [clearance 150 L/h] as compared to 5.8 hours [clearance 260 L/h] in healthy subjects). No effect on C_{max} or T_{max} was observed after a single dose.

After intravenous administration to patients with hepatic impairment, the elimination half-life of butorphanol was approximately tripled and total body clearance was approximately one half (half-life 16.8 hours, clearance 92 L/h) compared to healthy subjects (half-life 4.8 hours, clearance 175 L/h). The exposure of hepatically impaired patients to butorphanol was significantly greater (about 2-fold) than that in healthy subjects. Similar results were seen after nasal administration. No effect on C_{max} or T_{max} was observed after a single intranasal dose.

For further recommendations refer to **PRECAUTIONS: Hepatic and Renal Disease, Drug Interactions**, and Geriatric Use sections and to the **CLINICAL PHARMACOLOGY: Individualization of Dosage**section below.

Clinical Trials

The effectiveness of opioid analgesics varies in different pain syndromes.

Studies with butorphanol tartrate nasal spray have been performed in postoperative (general, orthopedic, oral, cesarean section) pain, in postepisiotomy pain, in pain of musculoskeletal origin, and in migraine headache pain (see below).

Use in the Management of Pain

Postoperative Pain

The analgesic efficacy of butorphanol tartrate nasal spray was evaluated (approximately 35 patients per treatment group) in a general and orthopedic surgery trial. Single doses of butorphanol tartrate nasal spray (1 or 2 mg) and IM meperidine (37.5 or 75 mg) were compared. Analgesia provided by 1 and 2 mg doses of butorphanol tartrate nasal spray was similar to 37.5 and 75 mg meperidine, respectively, with onset of analgesia within 15 minutes and peak analgesic effect within 1 hour. The median duration of pain relief was 2.5 hours with 1 mg butorphanol tartrate nasal spray, 3.5 hours with 2 mg butorphanol tartrate nasal spray and 3.3 hours with either dose of meperidine.

In a postcesarean section trial, butorphanol tartrate nasal spray administered to 35 patients as two 1 mg doses 60 minutes apart was compared with a single 2 mg dose of butorphanol tartrate nasal spray or a single 2 mg IV dose of butorphanol tartrate injection (37 patients each). Onset of analgesia was within 15 minutes for all butorphanol tartrate regimens. Peak analgesic effects of 2 mg intravenous butorphanol tartrate injection and butorphanol tartrate nasal spray were similar in magnitude. The duration of pain relief provided by both 2 mg butorphanol tartrate nasal spray regimens was approximately 4.5 hours and was greater than intravenous butorphanol tartrate injection (2.6 hours).

Migraine Headache Pain

The analgesic efficacy of two 1 mg doses 1 hour apart of butorphanol tartrate nasal spray in migraine headache pain was compared with a single dose of 10 mg IM methadone (31 and 32 patients, respectively). Significant onset of analgesia occurred within 15 minutes for both butorphanol tartrate nasal spray and IM methadone. Peak analgesic effect occurred at 2 hours for butorphanol tartrate nasal spray and 1.5 hours for methadone. The median duration of pain relief was 6 hours with butorphanol tartrate nasal spray and 4 hours with methadone as judged by the time when approximately half of the patients remedicated.

In two other trials in patients with migraine headache pain, a 2 mg initial dose of butorphanol tartrate nasal spray followed by an additional 1 mg dose 1 hour later (76 patients) was compared with either 75 mg IM meperidine (24 patients) or placebo (72 patients). Onset, peak activity and duration were similar with both active treatments; however, the incidence of adverse experiences (nausea, vomiting, dizziness) was higher in these two trials with the 2 mg initial dose of butorphanol tartrate nasal spray than in the trial with the 1 mg initial dose.

Individualization of Dosage
Use of butorphanol in geriatric patients, patients with renal impairment, patient with hepatic impairment, and during labor requires extra caution (see below and the appropriate sections in **PRECAUTIONS**).
The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). If adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given.
The initial dose sequence outlined above may be repeated in 3 to 4 hours as required after the second dose of the sequence.
For the management of severe pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients additional doses should not be given for 3 to 4 hours. The incidence of adverse events is higher with an initial 2 mg dose (see **Clinical Trials**).
The initial dose sequence in elderly patients and patients with renal or hepatic impairment should be limited to 1 mg followed, if needed, by 1 mg in 90 to 120 minutes. The repeat dose sequence in these patients should be determined by the patient's response rather than at fixed times but will generally be no less than at 6 hour intervals (see PRECAUTIONS).

INDICATIONS AND USAGE
Butorphanol Tartrate Nasal Spray USP is indicated for the management of pain when the use of an opioid analgesic is appropriate.

CONTRAINDICATIONS
Butorphanol Tartrate Nasal Spray USP is contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride.

WARNINGS

Patients Dependent on Narcotics
Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.
Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

Drug Abuse and Dependence
Drug Abuse
Butorphanol tartrate, by all routes of administration, has been associated with episodes of abuse. Of the cases received, there were more reports of abuse with the nasal spray formulation than with the injectable formulation.
Physical Dependence, Tolerance, and Withdrawal
Prolonged, continuous use of butorphanol tartrate may result in physical dependence or tolerance (a decrease in response to a given dose). Abrupt cessation of use by patients with physical dependence may result in symptoms of withdrawal.
Note: Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence. (See **DRUG ABUSE AND DEPENDENCE** section below.)

PRECAUTIONS

General
Hypotension associated with syncope during the first hour of dosing with butorphanol tartrate nasal spray has been reported rarely, particularly in patients with past history of similar reactions to opioid analgesics. Therefore, patients should be advised to avoid activities with potential risks.

Head Injury and Increased Intracranial Pressure
As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control
Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease
In patients with hepatic or renal impairment, the initial dose sequence of butorphanol tartrate nasal spray should be limited to 1 mg followed, if needed, by 1 mg in 90 to 120 minutes. The repeat dose sequence in these patients should be determined by the patient's

response rather than at fixed times but will generally be at intervals of no less than at 6 hours (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**and**Individualization of Dosage**section).

Cardiovascular Effects

Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk (see **CLINICAL PHARMACOLOGY**).

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Use in Ambulatory Patients

1. Opioid analgesics, including butorphanol, impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Effects such as drowsiness or dizziness can appear, usually within the first hour after dosing. These effects may persist for varying periods of time after dosing. Patients who have taken butorphanol should not drive or operate dangerous machinery for at least 1 hour and until the effects of the drug are no longer present.
2. Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with drugs that affect the central nervous system (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects such as drowsiness, dizziness and impaired mental function.
3. Butorphanol is one of a class of drugs known to be abused and thus should be handled accordingly (see Drug Abuse and Dependence section).
4. Patients should be instructed on the proper use of butorphanol tartrate nasal spray (see PATIENT INSTRUCTIONS and MEDICATION GUIDE).

Drug Interactions

Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

In healthy volunteers, the pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal spray were not affected by the coadministration of a single 6 mg subcutaneous dose of sumatriptan. However, in another study in healthy volunteers, the pharmacokinetics of butorphanol were significantly altered (29% decrease in AUC and 38% decreases in C_{max}) when a 1 mg dose of butorphanol tartrate nasal spray was administered 1 minute after a 20 mg dose of sumatriptan nasal spray. (The two drugs were administered in opposite nostrils.) When the butorphanol tartrate nasal spray was administered 30 minutes after the sumatriptan nasal spray, the AUC of butorphanol increased 11% and C_{max} decreased 18%.

In neither case were the pharmacokinetics of sumatriptan affected by coadministration with butorphanol tartrate nasal spray. These results suggest that the analgesic effect of butorphanol tartrate nasal spray may be diminished when it is administered shortly after sumatriptan nasal spray, but by 30 minutes any such reduction in effect should be minimal.

The safety of using Butorphanol Tartrate Nasal Spray and IMITREX®[1] (sumatriptan) Nasal Spray during the same episode of migrane has not been established. However, it should be noted that both products are capable of producing transient increases in blood pressure.

The pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal spray were not affected by the coadministration of cimetidine (300 mg QID). Conversely, the administration of butorphanol tartrate nasal spray (1 mg butorphanol QID) did not alter the phamacokinetics of a 300 mg dose of cimetidine.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

The fraction of butorphanol tartrate nasal spray absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if butorphanol tartrate nasal spray is administered concomitantly with, or immediately following, a nasal vasoconstrictor.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Information for Patients

See Use in Ambulatory Patients subsection above, and also see the Patient Instruction Leaflet and Medication Guide.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in mice and rats given butorphanol tartrate in the diet up to 60 mg/kg/day (180 mg/m^2 for mice and 354 mg/m^2 for rats). There was no evidence of carcinogenicity in either species in these studies.

Butorphanol was not genotoxic in ***S. typhmurium*** or ***E. coli*** assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/m^2) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/m^2) subcutaneous dose.

Pregnancy

Teratogenic Effects

Category C
Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. However, pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/m^2) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (360 mg/m^2) and 60 mg/kg/oral (720 mg/m^2) also showed higher incidences of post-implantation loss in rabbits.

There are no adequate and well-controlled studies of butorphanol tartrate in pregnant women before 37 weeks of gestation. Butorphanol tartrate should be used during pregnancy only if the potential benefit justifies the potential risk to the infant.

Labor and Delivery
Butorphanol tartrate nasal spray is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

Nursing Mothers
Butorphanol has been detected in milk following administration of butorphanol tartrate injection to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 mcg/L of milk in a mother receiving 2 mg IM four times a day). Although there is no clinical experience with the use of butorphanol tartrate nasal spray in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

Pediatric Use
Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use
Of the approximately 1700 patients treated with butorphanol tartrate nasal spray in clinical studies, 8% were 65 years of age or older and 2% were 75 years or older.
Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65 years (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**section). Elderly patients may be more sensitive to the side effects of butorphanol. In clinical studies of butorphanol tartrate nasal spray, elderly patients had an increased frequency of headache, dizziness, drowsiness, vertigo, constipation, nausea and/or vomiting, and nasal congestion compared with younger patients. There are insufficient efficacy data for patients >65 years to determine whether they respond differently from younger patients.
Initially a 1 mg dose of butorphanol tartrate nasal spray should generally be used in geriatric patients and 90 to 120 minutes should elapse before administering a second 1 mg dose, if needed (see **CLINICAL PHARMACOLOGY:Individualization of Dosage**section).
Butorphanol and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

Clinical Trial Experience
A total of 2446 patients were studied in premarketing clinical trials of butorphanol. Approximately half received butorphanol tartrate injection with the remainder receiving butorphanol tartrate nasal spray. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.
The adverse experiences described below are based on data from short-term and long-term clinical trials in patients receiving butorphanol by any route. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo-treated patients in controlled trials.
The most frequently reported adverse experiences across all clinical trials with butorphanol tartrate injection and butorphanol tartrate nasal spray were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with butorphanol tartrate nasal spray only, nasal congestion (13%) and insomnia (11%) were frequently reported.
The following adverse experiences were reported at a frequency of 1% or greater in clinical trials, and were considered to be probably related to the use of butorphanol.
Body as a Whole: asthenia/lethargy, headache, sensation of heat

Cardiovascular: vasodilation, palpitations
Digestive: anorexia, constipation, dry mouth, nausea and/or vomiting, stomach pain
Nervous: anxiety, confusion, dizziness, euphoria, floating feeling, insomnia, nervousness, paresthesia, somnolence, tremor
Respiratory: bronchitis, cough, dyspnea, epistaxis, nasal congestion, nasal irritation, pharyngitis, rhinitis, sinus congestion, sinusitis, upper respiratory infection
Skin and Appendages: sweating/clammy, pruritus
Special Senses: blurred vision, ear pain, tinnitus, unpleasant taste
The following adverse experiences were reported with a frequency of less than 1% in clinical trials and were considered to be probably related to the use of butorphanol.
Cardiovascular: hypotension, syncope
Nervous: abnormal dreams, agitation, dysphoria, hallucinations, hostility, withdrawal symptoms
Skin and Appendages: rash/hives
Urogenital: impaired urination
The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term butorphanol tartrate nasal spray trials and under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.
Body as a Whole: edema
Cardiovascular: chest pain, hypertension, tachycardia
Nervous: depression
Respiratory: shallow breathing

Postmarketing Experience
Postmarketing experience with butorphanol tartrate nasal spray and butorphanol tartrate injection has shown an adverse event profile similar to that seen during the premarketing evaluation of butorphanol by all routes of administration. Adverse experiences that were associated with the use of butorphanol tartrate nasal spray or butorphanol tartrate injection and that are not listed above have been chosen for inclusion below because of their seriousness, frequency of reporting, or probable relationship to butorphanol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These adverse experiences include apnea, convulsion, delusion, drug dependence, excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements, overdose, and vertigo. Reports of butorphanol overdose with a fatal outcome have usually but not always been associated with ingestion of multiple drugs.

DRUG ABUSE AND DEPENDENCE
Butorphanol tartrate nasal spray is listed in Schedule IV of the Controlled Substances Act (CSA).
Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence with butorphanol tartrate. Special care should be exercised in administering butorphanol to patients with a history of drug abuse or to patients receiving the drug on a continuous basis for an extended period.

Clinical Trial Experience
In all clinical trials, less than 1% of patients using butorphanol tartrate nasal spray had experiences that suggested the development of physical dependence or tolerance. Much of this information is based on experience with patients who did not have prolonged continuous exposure to butorphanol tartrate nasal spray. However, in one controlled clinical trial where patients with chronic pain from nonmalignant disease were treated with butorphanol tartrate nasal spray (n=303) or placebo (n=99) for up to 6 months, overuse (which may suggest the development of tolerance) was reported in nine (2.9%) patients receiving butorphanol tartrate nasal spray and no patients receiving placebo. Probable withdrawal symptoms were reported in eight (2.6%) patients using butorphanol tartrate nasal spray and no patients receiving placebo in the chronic nonmalignant pain study. Most of these patients abruptly discontinued butorphanol tartrate nasal spray after extended use or high doses. Symptoms suggestive of withdrawal included anxiety, agitation, tremulousness, diarrhea, chills, sweats, insomnia, confusion, incoordination, and hallucinations.

Postmarketing Experience
Butorphanol tartrate has been associated with episodes of abuse and dependence. Of the cases received, there were more reports of abuse with the nasal spray formulation than with the injectable formulation.

OVERDOSAGE

Clinical Manifestations
The clinical manifestations of butorphanol overdose are those of opioid drugs in general. Consequences of overdose vary with the amount of butorphanol ingested and individual response to the effects of opiates. The most serious symptoms are hypoventilation, cardiovascular insufficiency, coma, and death. Butorphanol overdose may be associated with ingestion of multiple drugs (see **ADVERSE REACTIONS: Postmarketing Experience**section).

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment
The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.
The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.
In managing cases of suspected butorphanol overdosage, the possibility of multiple drug ingestion should always be considered.

DOSAGE AND ADMINISTRATION
Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, the use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, in patients with hepatic or renal disease, or in labor requires extra caution (see PRECAUTIONS section and Individualization of Dosage in **CLINICAL PHARMACOLOGY**section). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

Use for Pain
The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given.
The initial dose sequence outlined above may be repeated in 3 to 4 hours as required after the second dose of the sequence.
Depending on the severity of the pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients single additional 2 mg doses should not be given for 3 to 4 hours.

Use in Balanced Anesthesia
The use of butorphanol tartrate nasal spray is not recommended because it has not been studied in induction or maintenance of anesthesia.

Labor
The use of butorphanol tartrate nasal spray is not recommended as it has not been studied in labor.

Safety and Handling
Butorphanol tartrate nasal spray is an open delivery system with increased risk of exposure to health care workers.
In the priming process, a certain amount of butorphanol may be aerosolized; therefore, the pump sprayer should be aimed away from the patient or other people or animals.
The disposal of Schedule IV controlled substances must be consistent with State and Federal Regulations. The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED
Butorphanol Tartrate Nasal Spray USP is supplied in a child-resistant vial containing a 2.5 mL bottle of nasal spray solution (10 mg/mL) and a metered-dose spray pump with protective clip and dust cover, a bottle of nasal spray solution, and a patient instruction leaflet and medication guide. On average, one bottle will deliver 14 to 15 doses if no repriming is necessary.
Butorphanol Tartrate Nasal Spray USP, 10 mg/mL
NDC 0054-3090-36: 2.5 mL bottle.

Storage Conditions
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
[1]IMITREX® is a registered trademark of Glaxo-Wellcome, Inc.

PHARMACIST ASSEMBLY INSTRUCTIONS FOR BUTORPHANOL TARTRATE NASAL SPRAY USP
The pharmacist will assemble butorphanol tartrate nasal spray prior to dispensing to the patient, according to the following instructions:
1. Open the child-resistant prescription vial and remove the spray pump and solution bottle.
2. Assemble butorphanol tartrate nasal spray by first unscrewing the white cap from the solution bottle and screwing the pump unit tightly onto the bottle. Make sure the clear cover is on the pump unit.

3. Return the butorphanol tartrate nasal spray bottle to the child-resistant prescription vial for dispensing to the patient with patient instruction leaflet and medication guide.

MEDICATION GUIDE
for BUTORPHANOL TARTRATE NASAL SPRAY USP, 10 mg/mL
CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
What is the most important information I should know about ButorphanolTartrate Nasal Spray USP?
• Your doctor has prescribed butorphanol tartrate nasal spray to treat your pain. The medication in butorphanol tartrate nasal spray belongs to a group of medicines that is known to cause dependence and abuse. Butorphanol tartrate nasal spray causes these effects only in a small number of patients. However, because it can have these effects, it is VERY IMPORTANT that you not use butorphanol tartrate nasal spray more often or in larger doses than your doctor has instructed. Also, it is important to have regular checkups with your doctor to ensure that you're using butorphanol tartrate nasal spray correctly. The longer you use butorphanol tartrate nasal spray, the greater your risk of getting dependent on it.
• Because butorphanol tartrate nasal spray may make you feel sleepy or dizzy, do not drive or operate dangerous machinery, e.g., automobiles until you can no longer feel the effects of the drug. Also, do not drink alcohol while using butorphanol tartrate nasal spray because it may worsen any side effects.
What is Butorphanol Tartrate Nasal Spray USP?
Butorphanol tartrate nasal spray is an opioid narcotic pain reliever that is used for the relief of pain when the use of an opioid pain medication is appropriate. Butorphanol tartrate nasal spray comes in the form of a nasal spray. One spray of butorphanol tartrate nasal spray is quickly absorbed in the nasal passages.
What do I need to know about using a strong opioid narcotic pain reliever suchas Butorphanol Tartrate Nasal Spray USP?
Butorphanol tartrate nasal spray has been reported to be abused. Do not use butorphanol tartrate nasal spray more often or in larger doses than instructed by your doctor. Follow your doctor's instructions exactly and have regular checkups with your doctor when using butorphanol tartrate nasal spray to ensure you are using butorphanol tartrate nasal spray properly.
Who should not take Butorphanol Tartrate Nasal Spray USP?
Butorphanol tartrate nasal spray should not be used if you have ever had an allergic reaction to the active ingredient, butorphanol, or if you are allergic to benzethonium chloride, a preservative in butorphanol tartrate nasal spray. Butorphanol tartrate nasal spray should not be used by patients less than 18 years old.
Butorphanol has been found in the breast milk of women who are using butorphanol tartrate nasal spray. Therefore, butorphanol tartrate nasal spray should not be used by patients who are breastfeeding. Patients over the age of 65 years may need less butorphanol tartrate nasal spray than younger patients.
You should not use butorphanol tartrate nasal spray if you are dependent on another narcotic medicine. Dependence is when you need the medicine and you can't perform normally unless you are taking it.
How should I take Butorphanol Tartrate Nasal Spray USP?
Use butorphanol tartrate nasal spray only as directed by your doctor. Never use butorphanol tartrate nasal spray more often or in larger doses than instructed by your doctor. Since you may experience sleepiness or dizziness, use butorphanol tartrate nasal spray in a comfortable location where you can lie down if necessary.
Usual Dosing
If your doctor prescribed a **1 mg dose** of butorphanol tartrate nasal spray for relief of pain:
• Spray ***one*** **spray** into ***one*** nostril – one spray is a 1 mg dose. This is the most common initial dose.
If prescribed by your doctor, a second spray may be taken 60 to 90 minutes after the first if needed for pain relief. If instructed by your doctor, the above sequence may be repeated every 3 to 4 hours as needed for pain relief. If your pain hasn't lessened or it becomes worse, please contact your doctor immediately.
If your doctor prescribed a **2 mg dose** of butorphanol tartrate nasal spray for relief of pain:
• Spray ***one*** **spray** in **each** nostril – two sprays equal a 2 mg dose. If instructed by your doctor, this dose of butorphanol tartrate nasal spray may be repeated every 3 to 4 hours as needed for pain relief. If your pain hasn't lessened or it becomes worse, please contact your doctor immediately.
If you have liver or kidney disease, you may need to take butorphanol tartrate nasal spray less often or in a lower dose. Elderly patients may also need to take a lower dose of butorphanol tartrate nasal spray.
Use and Storage of Nasal Spray Unit
Your pharmacist will assemble the nasal spray unit. However, you must prime the unit before using it the first time and if it has not been used for 48 hours or longer. **NOTE: VIALS DO NOT APPEAR "FULL." THEY ARE PREFILLED TO DELIVER ONAVERAGE 14 TO 15 ONE (1) MG DOSES.** If you only use butorphanol tartrate nasal spray occasionally and need to reprime it each time, the vial will deliver an average of 8 to 10 doses of butorphanol tartrate nasal spray. **See additional instructionsbelow for priming and using the spray unit.**
What should I avoid while taking Butorphanol Tartrate Nasal Spray USP?
• Because butorphanol tartrate nasal spray may make you feel sleepy or dizzy, do not drive or operate dangerous machinery, e.g., automobiles until you no longer feel the effects of the drug.
• Do not drink alcohol while using butorphanol tartrate nasal spray because it may worsen drowsiness, dizziness and your general ability to function appropriately.

• Some medications cannot be taken with butorphanol tartrate nasal spray because of unwanted side effects. Before you begin using butorphanol tartrate nasal spray, as well as while you are using it, be sure to tell your doctor about any and all other drugs you are taking, including those sold without a prescription (over-the-counter). Do not take any other medicine, including any over-the-counter medicine, unless directed to do so by a doctor who knows you are using butorphanol tartrate nasal spray.
• Because butorphanol tartrate nasal spray may cause harm to an unborn child, tell your doctor if you are pregnant or planning to become pregnant.
• Because small amounts of butorphanol tartrate may appear in breast milk, be sure to consult with your doctor if you are nursing an infant.
• Because of butorphanol tartrate nasal spray's potential to cause dependence or abuse, be sure to tell your doctor if you ever had a problem with overuse of drugs or alcohol.

What are the possible side effects of Butorphanol Tartrate Nasal Spray USP?

The type and frequency of side effects experienced by patients taking butorphanol tartrate nasal spray are those commonly seen with opioid narcotic pain relievers. The most frequently reported side effects in studies with butorphanol tartrate were drowsiness, dizziness, nausea and/or vomiting. In studies where patients used butorphanol tartrate nasal spray for up to 6 months, nasal congestion and difficulty sleeping were frequently reported.

Butorphanol tartrate nasal spray may affect your breathing. This side effect is serious but unlikely if butorphanol tartrate nasal spray is taken as instructed.

Notify your doctor immediately if you experience shortness of breath or other difficulty breathing.

Butorphanol tartrate nasal spray may affect your blood pressure or your heart rate. **Notify your doctor immediately if you feel lightheaded, have an irregularheartbeat or have headaches that you did not have before you started takingbutorphanol tartrate nasal spray.**

Side effects other than those listed above have occurred in some patients. For example, the following side effects have been reported rarely, but may be disturbing if they do occur: visual blurring, dysphoria (feeling of sadness, unpleasantness, or discomfort), floating feeling, and hallucinations. Notify your doctor or pharmacist if any side effects persist or become troublesome.

What do I do if someone takes an overdosage of Butorphanol Tartrate NasalSpray USP?

If you suspect that someone may have taken an overdosage of this medicine, contact your local poison control center or emergency room immediately.

This medication was prescribed for your current condition. Do not use butorphanol tartrate nasal spray for another condition or give the drug to others. Keep butorphanol tartrate nasal spray and all medicines out of the reach of children. Discard any unused portion of the medicine by removing the cap, rinsing the bottle and spray assembly under the water faucet, and disposing the parts in a waste can where children cannot easily get to them.

This summary does not include everything there is to know about butorphanol tartrate nasal spray. Medicines are sometimes prescribed for uses other than those listed. If you have questions or concerns, or want more information about butorphanol tartrate nasal spray, your doctor and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace a careful discussion with your doctor.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

KEEP OUT OF THE REACH OF CHILDREN.

PATIENT INSTRUCTIONS
for BUTORPHANOL TARTRATE NASAL SPRAY USP, 10 mg/mL

PATIENT INSTRUCTIONS

Take medication as directed by your physician. For proper use of the nasal spray, read the following instructions carefully.

NOTE: VIALS DO NOT APPEAR "FULL." THEY ARE PRE-FILLED TO DELIVER ON AVERAGE 14 TO 15 ONE (1) MG DOSES. (THE USUAL DOSE IS 1 MG-ONE SPRAY IN ONE NOSTRIL.)

THE UNIT MUST BE PRIMED WITH ONE OR TWO STROKES IF NOT USED FOR 48 HOURS OR LONGER.

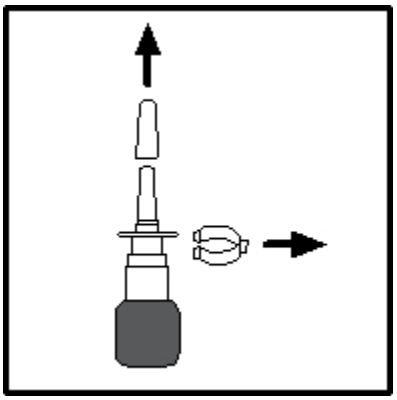
Note: With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8 to 10 doses of butorphanol tartrate nasal spray.

When not in use, store spray unit in child-resistant container. Butorphanol tartrate nasal spray should not be used by anyone other than the person for whom it was prescribed. To prevent this, and to reduce the chance of children taking the drug it is important to dispose of any excess butorphanol tartrate nasal spray just as soon as it is no longer needed.

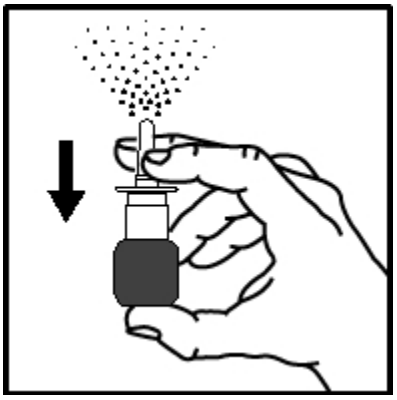
The best way to safely dispose of the unit is to unscrew the cap, rinse the bottle and spray assembly under the water faucet, and dispose of the parts in a waste can where children cannot easily get to them.

Figure 1

1. Blow nose gently to clear both nostrils.
Figure 2

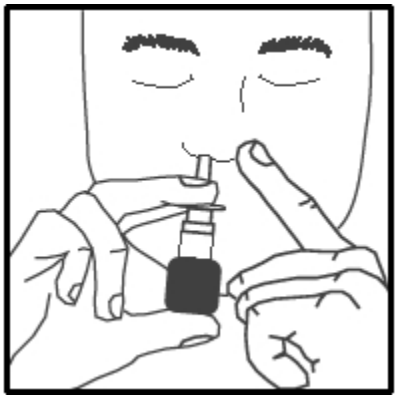


2. Pull clear cover off pump unit. Remove protective clip from neck of pump unit.
Figure 3



3. Prime butorphanol tartrate nasal spray by placing nozzle between first and second finger with thumb on the bottom of bottle. Pump sprayer unit FIRMLY and QUICKLY until a fine spray appears (up to 7 to 8 strokes).
Figure 4

4. Insert spray tip approximately 1 cm (width of small finger) into one nostril, pointing the tip toward the back of the nose.
Figure 5



5. Close other nostril with your forefinger and tilt head slightly forward.
Figure 6

6. Pump spray unit firmly and quickly by pushing down on the “finger grips” of the pump unit and against the thumb at the bottom of the bottle. Sniff gently with your mouth closed.
Figure 7

7. After spraying, remove pump unit from nose. Tilt your head backwards and sniff gently a few more seconds.
8. Your doctor will tell you whether a two spray dose is needed. If needed, administer a second spray in the other nostril, following steps 4 through 7. Replace protective clip and clear cover, respectively, (Fig. 2) after each dose.

USUAL DOSE: ONE Spray. Spray ONLY ONCE into ONLY ONE nostril.
DO NOT spray into both nostrils unless directed by your doctor.
DO NOT repeat sooner than directed by your doctor.

10001972/03 Revised February 2009

PACKAGE LABEL - BUTORPHANOL TARTRATE NASAL SPRAY USP, CIV, 10 MG/ML
NDC 0054-3090-36 - 2.5 mL Bottle.
Rx Only
Roxane Laboratories, Inc
Bottle Label

Carton Label

Revised: 10/2009 Distributed by: Roxane Laboratories, Inc